GENERAL ⚡ ELECTRIC

NASA CR.

147674

HOUSTON, TEXAS	TECHNICAL INFORMATION RELEASE	TIR 741-MED-4021

FROM R. C. Croston, Ph.D.	TO J. A. Rummel, Ph.D./DB6		

DATE 8/15/74	WORK ORDER REF: MA-252T	WORK STATEMENT PARA: NAS9-12932	REFERENCE:

SUBJECT

Final Report

(NASA-CR-147674)   A LONG TERM MODEL OF   N79-24636
CIRCULATION   Final Report, 1973-1974
(General Electric Co.)   59 p HC A04/MF A01
   CSCL 06P   Unclas
                                   G3/52   22231

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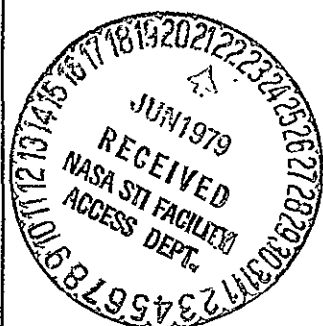
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FINAL REPORT

A LONG TERM MODEL OF

CIRCULATION

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I. INTRODUCTION

The human body is so complex that all those who study it must utilize models
to relate and interpret the vast amount of available experimental data. This
has been true from almost the earliest days of modern physiology and medi-
cine. Until recently these models of whole-body function have been mostly
qualitative with many being entirely verbal, but with the rise in availability
of computer systems, more quantitative modeling approaches have begun to
appear. These quantitative human simulation models have been most success-
ful at the subsystem level where the circulatory system, respiratory system,
renal system, and thermoregulatory system, among others, have all been
treated in varying detail. Such a quantitative approach offers several distinct
advantages over the more traditional, essentially qualitative, modeling struc-
ture. First, alternative hypotheses of function may be subjected to quantitative
comparison which often suggests the more significant of the hypotheses.
Second, the interaction between various subsections of a model become more
apparent in a quantitative formulation. Third, quantitative modeling allows
one to more readily identify significant unresolved problems relevant to a
complete understanding of the system under study. When coupled with a
viable experimental program this produces an iterative protocol, alternately
using modeling and experiment, to converge toward the truth. Fourth, a
quantitative approach is a valuable teaching tool, conveying both concepts and
detailed function of a system. Fifth, the more mathematical type of analysis
allows a calculation of quantitative values of variables that are difficult or
impossible to measure. Sixth, a quantitative modeling approach has a pre-
dictive capacity that is important when direct experiments are difficult to per-
form. This predictive ability usually is more significant than the correspond-
ing predictiveness associated with a more qualitative approach.

For the above reasons a quantitative approach to modeling human physiological
function with a view towards ultimate application to long duration space flight
experiments has been undertaken and is now in progress. For the first time,

data has been obtained on the effect of weightlessness on certain aspects of human physiological function over relatively extended periods (1-3 months). The biomedical investigations of Project Skylab are beginning to reveal an interesting pattern of adaptive phenomena occurring in the tightly related areas of body fluid volumes, electrolyte and water balance, and circulatory function. The experimental situation met in Project Skylab is complex due to the difficulty in separating the effects of possible lessened activity (deconditioning) from the hypogravic effects. This difficulty is compounded by the fact that extrapolation and prediction are most desirable features, while at the same time additional, possibly clarifying, experiments are now impossible to perform, at least for several years. It is in just such a situation that modeling may play an important role.

This report summarizes tasks accomplished in the modeling area by the author during 1973-74. Section II concerns modifications of the long-term circulatory model originally developed by Guyton (1, 2). Section III discusses design considerations for bilateral interface models whereby dual functioning of major subsystem models may obtain. The final section, Section IV, addresses itself to the construction of a functioning whole-body model as well as the testing of the model versus available data (model verification).

II.   MODIFICATIONS IN THE GUYTON MODEL

The circulatory model originally developed by Guyton has been modified and performance improved in several respects. The main modifications concerned the renin-angiotensin system, the baroreceptor system, stress relaxation of the vasculature, autoregulation of muscle blood flow, and the red cell system. Consideration has also been given to the possible inclusion of gravitational effects and incorporation of an acid-base homeostatic system in the present model.

Renin-Angiotensin System

The original version of the Guyton model did not possess an adequate representation of the renin-angiotensin system. In particular, renin secretion per se was not present, and the model did not respond correctly to low-level angiotensin II infusion. The previous model contained what was essentially a black box with angiotensin level dependent on tubular sodium flow. In order to extend the range of applicability of the model a more physiologically oriented section has replaced the previous black box model. A flow chart of the added system is given in Figure 1. The modifications were incorporated in SUBROUTINE HORMON in place of lines 25-34 inclusive. New coding was inserted in this place as follows:

25	CALL FUNCTN(PAR, RNS, FUN8)
26	RSR=300.*REK*RNS*(1.-ANGS-B*(GFR*CNA-17.75))
27	IF(RSR.LT.0.)) RSR=0.0
28	RT= RT+ (RSR-CRA*RT)*(1.-EXP(-I/RNK))
29	RC = RT/VP
30	AN1=CAIV+CAS*RC
31	AN2=AN2+(AN1-CAA*AN2)*(1.-EXP(-I/AKA))
32	ANC=AN2/VP/ANCN
33	ANM=ANMM-AN3*EXP(-ANC/ANTC)
34	IF(ANM.LT.0.5) ANM=0.5
35	ANSS=A*(ANC-1.)
36	ANGS=ANGS+(ANSS-ANGS)*I/ANGT
37	ANK=ANM
38	IF(ANK.LT.1.)ANK=1.

In addition, line 16 of SUBROUTINE MISC2 was modified to read

16	STH=(Z10-POT)*Z11*(1.+ATH*(ANC-1.)).

Lines 11, 12, and 23 of SUBROUTINE KIDNEY were changed to

11   AAR=31.67*VIM*(AUM*ARF+1.-ARF)*GF3*(1.+ANAR*(ANM-1.))

12   RR=AAR+51.66*VIM*(1.+ANER*(ANM-1.))

23   TRR=GFR*(0.8+GP1*(ANK-1.))/(1.+GP1*(ANK-1.))+.025*REK-.001*REK/AM/AHM

The changes in SUBROUTINE HORMON have the following significance.

Line 25.   Calculation of renin secretion per gram of kidney (RNS) based on renal arterial pressure (PAR). (Figure 2)

Lines 26-27.   Calculation of total renin secretion rate (RSR) limited by 0 based on renin secretion per gram of kidney (RNS), effective kidney mass (300.*REK), angiotensin effect (ANGS), and tubular sodium flow (GFR*CNA).

Line 28.   Calculation of total renin amount (RT) by integration of production rate (RSR) minus destruction rate (CRA*RT) with integrative damping factor RNK.

Line 29.   Calculation of plasma renin concentration (RC) by dividing total amount (RT) by plasma volume (VP).

Line 30.   Calculation of the production rate of angiotensin II (AN1) from the infusion rate (CAIV) and the normal production from renin.

Line 31.   Integration of net production rate of angiotensin II to yield angiotensin amount (AN2).

Line 32.   Calculation of ratio of plasma angiotensin II concentration to normal (ANC) by dividing angiotensin amount by plasma volume (VP) and normal angiotensin II plasma concentration (ANCN).

Lines 33-34.   Empirical calculation of the effect of angiotensin II (ANM) from a dose-response curve relating to angiotensin concentration (ANC).

Line 35.   Calculation of steady-state suppressive effect of angiotensin on renin production (ANSS).

Line 36.   Calculation of actual suppressive effect of angiotensin II on renin (ANGS) by a slow approach to ANSS with time constant ANGT.

Lines 37-38.   The effect of angiotensin on tubular reabsorption (ANK) is limited to values greater than or equal to 1.

In SUBROUTINE MISC2, the change allowed thirst and salt intake to depend on angiotensin II levels. In SUBROUTINE KIDNEY, lines 11 and 12 were modified to allow afferent and efferent arteriolar resistances to depend on angiotensin II effect (ANM) with sensitivities ANAR and ANER, respectively. Line 23 was modified to increase tubular reabsorption of water (TRR) with high angiotensin levels.

Baroreceptor System

The baroreceptor system of the original Guyton model has been upgraded by direct inclusion of separate aortic and carotid effects and by separate inclusion of the autonomic influence on contractility of the heart and whole-body unstressed volume. Appropriate delays and resetting have been utilized. A flow chart for the modified system is given in Figure 3. The modifications were made in the program in the following areas. In SUBROUTINE AUTO lines 17-20 inclusive were replaced by

```
17      CALL FUNCTN(PA1,AUCB,FUN9)
18      CALL FUNCTN(PA1, AUAB,FUN10)
19      A1B = 1.+CCB*AUCB+CAB*AUAB
20      CONTINUE.
```

Line 36 was replaced by

```
36      CALL FUNCTN(PA1,AUH1,FUN11)
36A     AUH2=AUH1-AUH3
36B     AUH=AUH+(AUH2-AUH)*I2*6./Z8
36C     IF(STA.GT..00001)AUH=STA
```

and line 38 was replaced by

```
38      CALL FUNCTN(PA1,VOT1, FUN12)
38A     VOT2 = VOT1 - VOT3
38B     VOT= VOT+(VOT2-VOT)*I2*6./Z8
38C     IF(STA.GT..00001)VOT= 4.25.
```

In SUBROUTINE MISC1 the following lines were inserted after line 27.

27A   AUH3 = AUH3+(AUH2-1.)*I*AUK

27B   VOT3 = VOT3+(VOT2-4.25)*I*AUK.

The significance of these changes are as follows.   For SUBROUTINE AUTO

Lines 17-20.   Calculation of the contribution of the baroreceptors to auto-
nomic stimulation (A1B) based on graphical interpolation.
Both aortic (AUAB) and carotid (AUCB) are included with
relative sensitivities CAB and CCB.   (Figures 4 and 5)

Lines 36-36C.   Calculation of the autonomic effect on cardiac contractility
(AUH) by graphical interpolation (Figure 6) with a delay and
resetting mechanism.

Lines 38-38C.   Calculation of the total unstressed volume of the systemic
circulation based on graphical interpolation (Figure 7) with
a delay and resetting mechanism.

For SUBROUTINE MISC1

Lines 27A-27B.   Resetting mechanism for heart contractility (AUH3) and
unstressed volume (VOT3).

Vascular Stress Relaxation

Stress relaxation of the vascular system has been extended by the inclusion

of new components with different time constants for action.   These new com-

ponents are associated with six-hour and fourteen-day relaxation phenomena.

Changes were made in SUBROUTINE MISC1 where the following insertions

were made after line 11.

11A   V61=V61+(SR1*(VVE-.301)-V61-V71)/Z

11B   V71=V71+V61*(1.-EXP(-I/SRL))

11C   V62=SR2*(VVE-.301)-V72

11D   V72=V72+V62*I/SRM

11E   VVT=X6*VV7+X7*V71+X8*V72.

The significance of these changes are as follows:

Line 11A.   Calculation of the rate of progression of intermediate-term vascular stress relaxation (V61) by subtracting the reference venous volume (.301) from the excess venous volume (VVE). SR1 is the intensity of such stress relaxation.

Line 11B.   Calculates the stress-relaxation volume due to intermediate-term stress relaxation (V71) by integration of the rate of progression (V61) with time constant SRL.

Lines 11C-11D   Similar to the previous two lines except that the long-term effect (V72) is calculated.

Line 11E.   Calculation of total stress-relaxation volume (VVT) by taking a weighted sum of the three previously calculated effects.

Other Changes

Other changes were made in the basic model and these are included here for completeness.

In SUBROUTINE HEMO these changes are as follows. Line 21 was replaced by

```
21      VASO  =  0.116*VOT
21A     VAE   =  VAS-VASO.
```

Line 26 was replaced by

```
26      VRAO  =  0.0235*VOT
26A     VRE   =  VRA-VRAO.
```

Line 29 was replaced by

```
29      VPAO  =  0.072*VOT
29A     VPE   =  VPA-VPAO.
```

Line 36 was replaced by

```
36      VLAO  =  0.0941*VOT
36A     VLE   =  VLA-VLAO.
```

Lines 44–46 were replaced by

```
44      IF(ANU.LT..6)ANU=.6
45      VVE=VVS-0.694*VOT-(ANU-1.)*ANY
45A     VVSO=.694*VOT+VVT+(ANU-1.)*ANY
46      VV8=VVS-VVSO.
```

In SUBROUTINE MUSCLE line 24 was replaced by the following:

```
24      AMS   =  AMS+(POE-AMS)*(1.-EXP(-I/A4K))
25      POF   =  1.+POU*PDO
26      AM2   =  AM2+(POF-AM2)*I/A5K
27      AMM   =  AM2*AMS.
```

In SUBROUTINE CAPMBD line 26 was replaced by

```
26      VPD   =  VPD+(TVD-VTC+VTL-VUD-DFP-VPD+RTR-VIL)/Z1
27      VP    =  VP+VPD*I/Z3.
```

In SUBROUTINE IONS the following line was inserted after line 9.

```
9A      IF(KO.GT..00001)KOD=KO.
```

In SUBROUTINE KIDNEY lines 23–24 were replaced by

```
23      IF(DESC.GT.0.0) GO TO 151
24      VUGF=0.2*GFR
24A     GO TO 152
24B     151  VUGF=VUGF+(0.2*GFR-VUGF)*I/UOC
24C     152  VUD=VUGF/(1.+GP1*(ANK-1.))-0.025*REK+0.001*REK/AM/AHM
```

After line 25 the following line was inserted.

```
25A     IF(VOB.GT..00001) VUD=VOB.
```

After line 31 the following line was inserted.

```
31A     IF(NAO.GT..00001)NOD=NAO.
```

Line 32 was changed to read

32   NED=NID*STH-NOD+RNA.

In SUBROUTINE MISC1 the following line was added after line 19.

19A   IF(VINT.GT..00001)TVD=VINT.

The significance of these changes are as follows: The changes in SUBROUTINE HEMO allow a direct calculation of the unstressed volume of each vascular compartment (VASO, VRAO, VPAO, VLAO, VVSO) based on the total unstressed volume (VOT), angiotensin (ANU), and stress relaxation (VVT). In SUBROUTINE MUSCLE the change allowed an intermediate-term autoregulation term (AM2) to have an effect. In SUBROUTINE CAPMBD the change allowed the direct inclusion of a water infusion term (RTR) and an insensible loss term (VIL). In SUBROUTINE IONS the change allowed control of potassium excretion rate through KO. The changes in SUBROUTINE KIDNEY allowed a time delay in urinary output (through changes in DESC) and allowed control of urinary output through VOB and sodium excretion through NAO as well as controlled sodium infusion through RNA. The change in SUBROUTINE MISC1 allowed for control of drinking through VINT.

All new terms introduced into the model are defined in Appendix A. Normal steady-state values of these variables are given there as well.

Further Studies

Although the preceding changes were the only ones implemented, other systems were studied for possible inclusion in the Guyton model. These systems include a new acid-base homeostatic system, a modified red-cell model, and a mechanism with potential utility for the inclusion of gravitational effects.

Appendix B of this report contains a study report on acid-base homeostasis. This was prepared as a preliminary to actual insertion of some elements of

acid-base control in the Guyton model. Although there are many reasons why such an insertion would be desirable, it is recommended that the acid-base system not be added to the Guyton model at the present time. This recommendation is made because (1) such an addition is non-trivial and experiments should be conducted to obtain the proper quantitative information, (2) no direct experiments related to acid-base phenomena are part of Project Skylab, and (3) some elements of acid-base effects are already implicitly contained in certain control elements, particularly as regards autonomic stimulation. These latter implicit effects would have to be removed if an explicit formulation were to be inserted.

The red cell model presently utilized as a subsystem of the Guyton model is physiologically inaccurate in response to stimuli for production. The present model is based on non-muscle tissue PO_2 with a fall in PO_2 initiating increased production. Although the idea of using such a change in oxygen partial pressure to increase production is probably sound, the receptor site is probably located in the kidney, not the other non-muscle areas. Also the response in the present model leads to anemia whenever PO_2 changes due to a hypervolumic state are compensated for by flow increases. A replacement subsystem was investigated for red cell control which was based on a receptor site location in a constant flow, constant metabolizing area of the body, presumably a portion of the kidney. This new model is somewhat better than the former one, but improvements are intended shortly which will make the system even more realistic. At the time these improvements are made, the new section will be inserted in the original Guyton model.

Since the effect of gravity upon return from space on the cardiovascular system is of some interest, it might prove fruitful to incorporate gravitational effects into the Guyton model. At first glance, this might seem impossible since the Guyton model contains only five systemic volume compartments with no distinction made as to physical location. Buy by using

a three compartment model (upper body, trunk, lower body) the effect of
gravitational changes on appropriate variables may be simulated. These
effects include an average decrease in venous pressure at the right heart
due to standing, a hydrostatic pressure effect at the kidney, the gravitational
effect on capillary pressure, the gravitational effect on pressure at the baro-
receptor site, the effect of the muscle pump, and the effect of abdominal
compression.

Model Experiments

A series of experiments were run using the most recent version of the model
in an attempt to demonstrate validity of the changes made. These experiments
include low level angiotensin infusion, double Goldblatt clamp, and salt-induced
renoprival hypertension on both normal and baroreceptor denervated subjects.

Tables 1 – 4 contain the results of some of these experiments. In each case
the variables tabulated are extracellular fluid volume in liters (VEC), auto-
nomic effect, ratio to normal (AU), cardiac output in liters/min (QLO), mean
arterial pressure in mm Hg (PA), urinary output in ml/min (VUD), and
angiotensin II concentration, ratio to normal (ANC). These results compare
quite favorably with recent experiments (3). In each case the results repre-
sent an improvement over previous simulations using the former model
version. Certain other simulations in the particular area of infusions of
various types were also made (4, 5).

III. DESIGN CONSIDERATIONS FOR BILATERAL INTERFACE MODELS

Most physiological modeling has been concerned with function at the sub-system level, or with whole-body function of limited extent. In an effort to realistically extend modeling capabilities beyond this, an attempt has been made to design separate bilateral interface models each composed of a long-term circulatory model (Guyton) and one other of the three major models under study (thermoregulatory (6), respiratory (7), short-term circulatory (8)).

These design considerations will be discussed for each model in turn. The design will be purely qualitative with actual implementation introducing quantitation. Only the respiratory-circulatory combination included implementation.

Respiratory-Circulatory Interface

Let us assume that one has two different models of physiological function, each of which is designed specifically to simulate detailed function of different aspects of function. In general, each model will have overlap areas with the other, as well as non-overlapping areas. Each model may respond to the same as well as different stimulii. If the models are compatible in time as regards duration of feasible simulations, it may be quite possible to form a composite or bilateral model which offers advantage to each subsystem in effecting simulation.

To combine compatible models requires that all overlap areas be eliminated, that the effect of stimulii acting on one model be properly related to the other, and no non-overlapping areas act to yield contradictory results.

In the case of the respiratory and circulatory models, compatibility exists over the short term only (10-30 minutes). This limitation exists because of inherent weaknesses in the respiratory model. It is obvious that there must

be areas of overlap of these two models. In the respiratory model blood must flow to provide tissue oxygen and to remove excess carbon dioxide. In the circulatory model breathing of some sort must be present to oxygenate the available hemoglobin. In each case though, for these models, the elements of overlap consist of a fairly detailed version in one model and a relatively crude version of the same function in the other model. This made elimination of overlap fairly easy. It was decided to allow the circulatory model to determine all flows (except brain blood flow), all metabolic parameters (except brain oxygen consumption), and all factors related to total hemoglobin present. The respiratory system would determine the fractional saturation of hemoglobin in aortic blood, which the circulatory system uses, as well as all the other respiratory parameters not directly involved with the circulatory system.

The implementation of this scheme is presented in detail elsewhere (9, 10, 11), and will not be covered again here. Briefly, it was found that the models performed adequately during exercise, but not during other non-steady state perturbations. This might have been expected had the interfacial structure been subjected to a more critical examination. In particular, during exercise each model was capable of running independently of the other and crudely simulated the correct performance of the other model. So, it would be expected that the models would simulate exercise well when acting together. With the other forcings, like CO_2 inhalation, only one of the independent models was designed to handle the stimulation. New terms should have been added to the other model to represent the effect of this new driving force (e. g. , CO_2 exerts a local dilatory and central constrictory effect). Since this was not done, it might be expected that the overall system would respond improperly.

Consideration of design questions for this bilateral model has been very useful in emphasizing that at least three questions must be faced in combining even compatible models. The easiest problem to solve generally relates to elimination of overlap areas. The effect of neglect of stimulii on one model

acting directly on the other was well illustrated with CO_2 forcing. The
ability of non-overlapping areas acting to yield poor results is illustrated
by a bilateral heart failure experiment where the combined respiratory-
circulatory model was only utilized after independent circulatory stability
was obtained. The results are again poor, but this time because the circu-
latory model had abnormal fluid volumes and, undoubtedly should have had
abnormal bicarbonate concentrations in the blood and tissues.

Long Term-Short Term Circulatory Interface

Although the long term circulatory model (Guyton) is well-suited to the sim-
ulation of certain experimental situations relevant to the Skylab mission, some
pertinent experiments are difficult to simulate effectively with only a five
compartment systemic circulatory loop. In particular, one of the main Skylab
experiments pertaining to the circulatory system, the lower body negative
pressure (LBNP) experiment, presents some difficulty due to the lack of a
sufficient number of compartments. A model that performs adequately to sim-
ulate LBNP has been developed (8), but this model contains 28 systemic cir-
culatory compartments. This latter model also has various serious weaknesses
of its own, the most important of which concern the lack of fluid and protein
transfer into and out of the systemic compartment and the lack of a drinking
mechanism or functioning kidney. Thus, whenever fluid regulation is important,
tant, errors are likely. Because of these things, this large systemic model
is limited in application to short term experiments.

One solution to problems of the above type is to utilize the long term model to
compute fluid volume shifts and then to automatically define initial operating
conditions for the short term model. The short term model would then be
stimulated with local exercise, positional differentiation in a gravitational
field, or LBNP. The problems involved in accomplishing this type of bilateral
interface are related to the obvious non-uniqueness of the transition between

the models, and the fact that the controlling system for the short term model should be initialized also. Thus, if A-V muscle blood flow is set by a small model having only one muscle bed, how would the flow be distributed in a larger model with muscle beds contained in the arms, legs, and trunk? It turns out that such degrees of freedom must be chosen to correspond to known physiological conditions in the subject at the time the model-model interaction takes place. If there is a sparsity of known conditions, intuition must be used as a guide, just as in initial model development. It should be possible to combine computer experiments with known physiological experimental results and define the initialization procedure.

Automatic initialization of a compartmentalized model of systemic circulation should at the very least consist of volume initializations. Circulatory function without inclusion of adaptive phenomena is known to be highly sensitive to volume changes. Other important candidates for inclusion in initialization procedures pertain to flow or resistance changes, and to the state of the controlling system. The design of such an initialization scheme is complicated by the fact that each of these areas is affected by the other two. Thus, if volume increases, flow also increases, and the controller state changes. The problem lies in separating the effects sufficiently that a plan can be formulated to obtain a proper initialization. It is doubtful whether a single adjustment (like a volume change) can give the necessary model correspondence).

It is suggested that actual design of this interfacial system would best be done through implementation of a routine capable of transferring information between the two models and then to use a system of essentially trial and error to complete the linkage. The procedure might be as follows. Step 1: initialize total blood volume and unstressed volume. Step 2: change the autonomic effect to initialize heart rate. Step 3: change resistances to initialize flows. Step 4: repeat steps 2 and 3 until proper equilibrated values are obtained for volumes, flows, and pressures.

Thermoregulatory-Circulatory Interface

The thermoregulatory-circulatory interfacial design has much in common with the respiratory-circulatory interface discussed earlier in that a division of labor, of sorts, along physiological lines is possible. Thus, all blood flows should be extracted from the circulatory system, all heat flows should be computed from the thermoregulatory system. But in the complex response that pertains to thermal driving forces on both local and central controlling systems for blood flow, this division of labor is not so apparent. What is clear is that a certain amount of additional modeling on the subsystem level itself is necessary to be able to properly relate thermal stresses to the circulatory system. This is because of the fact that the two models were developed on quite different bases as regards the treatment of circulation. This makes it much more difficult to find analogous qualities of circulatory control in the models, and to correspondingly exchange information. Thus, design considerations must await further in-depth review of thermoregulatory function in terms of common cardiovascular function.

IV. DESIGN OF A WHOLE-BODY MODEL

A whole-body model is assumed to be a large-scale dynamic mathematical model of the human body capable of responding to both long and short term stresses of various kinds. These stresses may act on any one or any collection of the "subsystems" of which the model is composed. It is assumed that the stresses are well-defined in the sense that the model will be specifically designed to cope with each applied stress.

It is impossible to face the modeling problems that one must solve to construct this whole-body model without actually implementing the model. Design and implementation are so intertwined in a model of this size that it is actually wasteful of resources to try to develop specific detailed approaches until implementation. Instead, more is to be gained prior to actual implementation by considering alternative general approaches.

There are probably two main approaches to modeling a large system composed of (at least) two subsystems. First, each subsystem could be modeled independently, possibly by different people using different hypotheses. After each subsystem worked properly in some test situation(s), the subsystem models could be combined into a unit by restructuring or redesigning the subsystems to work together. Second, the system as a whole could be attacked and a cohesive model assembled utilizing a single non- contradictory set of hypotheses, and designed to function as a unit from the beginning. Although these two approaches might seem very different, if each is pursued properly, with the same goals in mind, the final results should be quite similar. In particular, it is probably not less work to follow the first path mentioned above since considerable effort could be spent in redesign considerations when subsystem models are combined. It would seem to be preferable only to study the components of a large system by subsystem analysis, but to model the whole system as a unit utilizing only the basic ideas on subsystem function, not subsystem structure per se. This is the recommendation made for the development of a whole-body model. By utilizing ideas and experience gained from a separate study of major body subsystems, it should be possible to construct a completely unified model which incorporates major system function in a cohesive way. It should be no more difficult to do this than to combine several models together in workable fashion for non-trivial simulation stress.

TABLE 1.

CONTINUOUS ANGIOTENSIN INFUSION

(Normal subject; Rate: 350 ng/min)

Time After Infusion	VEC	AU	QLO	PA	VUD	ANC
0.	15.05	1.0	5.12	102	1.	1.0
8 hr.	15.46	.84	4.99	116	.2	5.0
1 day	15.68	.80	5.27	126	1.5	4.3
3 days	15.19	.90	5.09	134	.9	4.6
7 days	15.30	.98	5.10	140	.9	4.6

TABLE 2.

CONTINUOUS ANGIOTENSIN INFUSION

(Baroreceptor Denervated Subject; Rate: 350 ng/min)

Time After Infusion	VEC	QLO	PA	VUD	ANC
0	15.05	5.15	102	1.0	1.0
8 hr.	15.42	5.09	142	0.6	5.0
1 day	15.35	5.14	143	1.0	4.7
3 days	15.31	5.09	142	0.9	4.6
7 days	15.33	5.08	142	0.9	4.6

TABLE 3.

GOLDBLATT HYPERTENSION

(Normal Subject; Renal Pressure Decrease: 50 mm Hg)

Time After Clamp	VEC	AU	QLO	PA	VUD	ANC
0	15. 06	1. 0	5. 09	101	1. 0	1. 0
8 hr.	15. 88	. 72	4. 95	126	0. 2	22.
1 day	15. 84	. 57	5. 60	139	1. 1	2. 7
3 days	15. 45	. 91	5. 51	149	0. 5	2. 0
7 days	15. 46	1. 0	5. 52	149	0. 5	1. 8

TABLE 4

GOLDBLATT HYPERTENSION

(Baroreceptor Denervated Subject; Renal Pressure Decrease: 50 mm Hg)

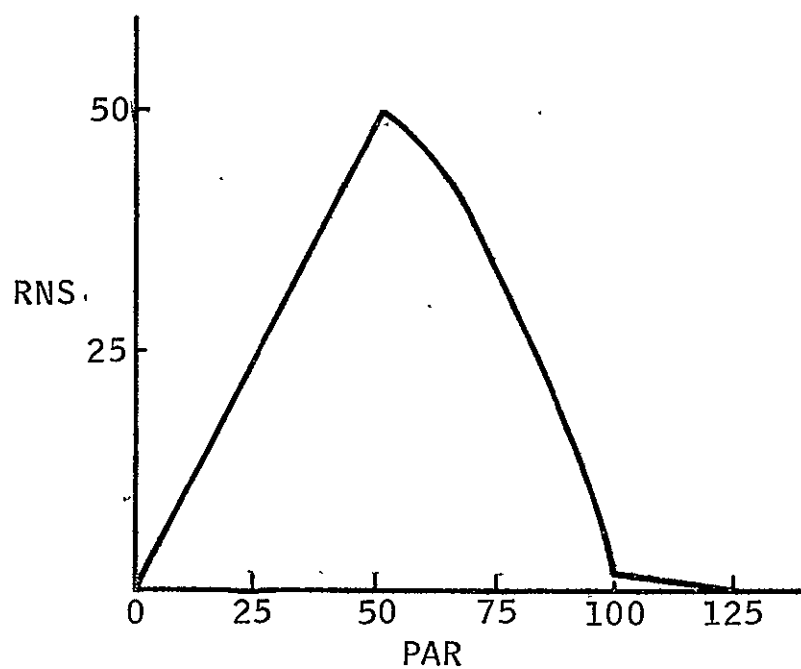| Time After Clamp	VEC	QLO	PA	VUD	ANC
0	15. 05	5. 16	102	1. 0	1. 0
8 hr.	15. 55	5. 02	156	0. 2	7. 5
1 day	15. 78	5. 65	149	0. 7	1. 7
3 days	15. 50	5. 56	149	0. 5	1. 7
7 days	15. 46	5. 58	150.	0. 5	1. 7

FIGURE 1. RENIN-ANGIOTENSIN SYSTEM

FIGURE 2. RELATION BETWEEN RENAL ARTERIAL PRESSURE (PAR)
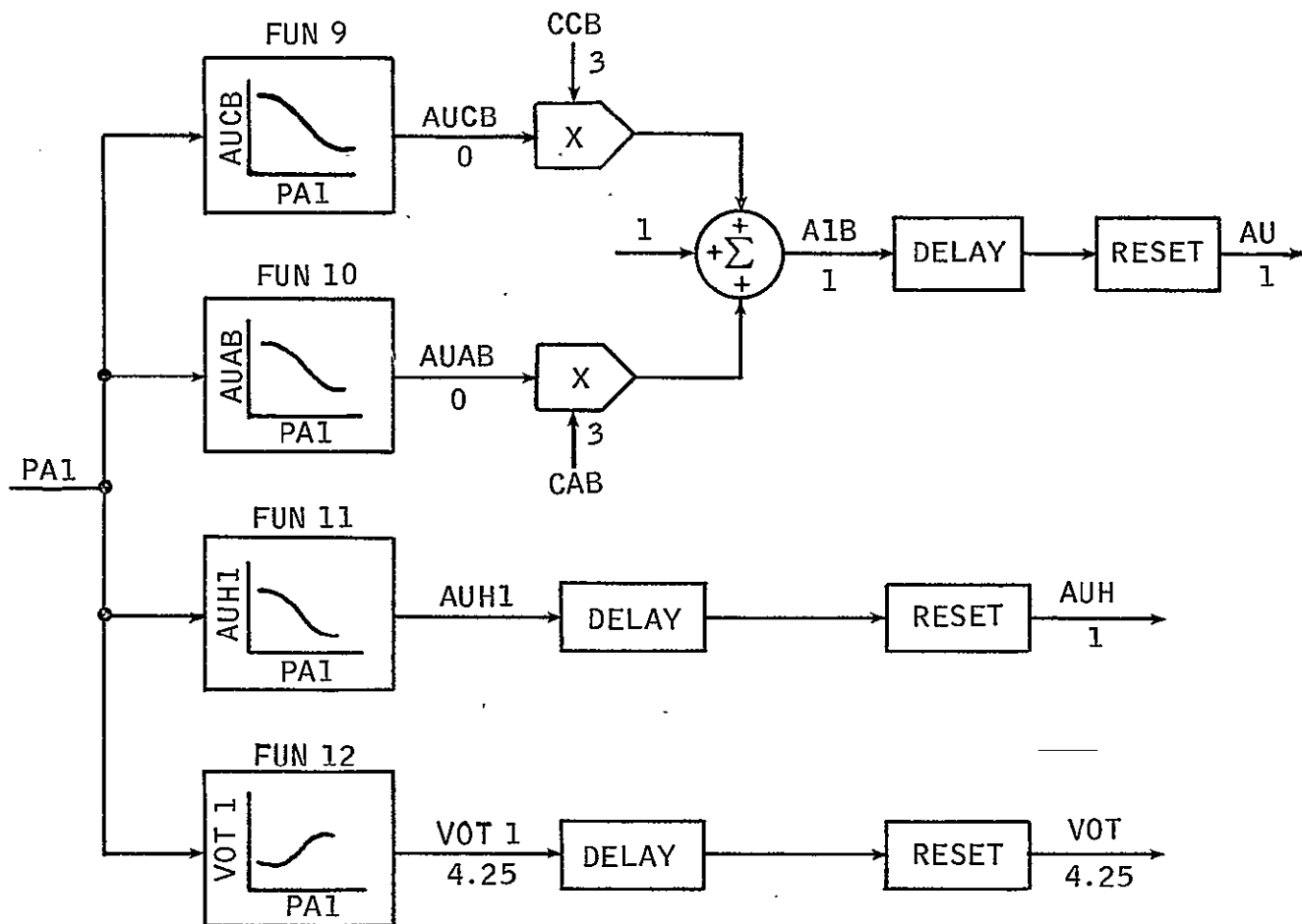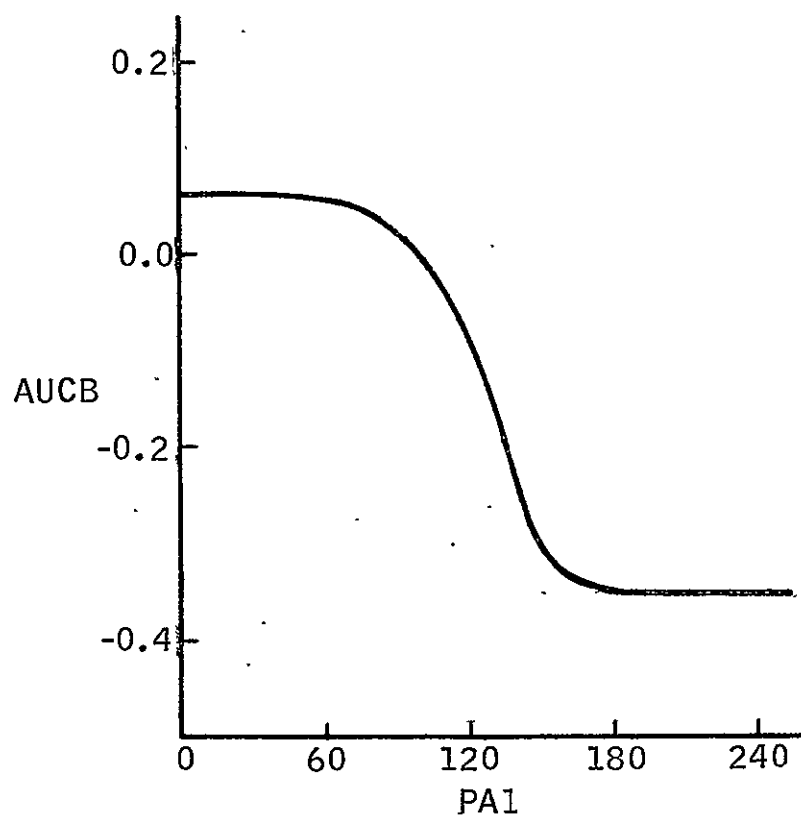AND RENIN SECRETION RATE PER GRAM OF KIDNEY(RNS).

FIGURE 3. BARORECEPTOR SYSTEM

FIGURE 4. RELATION BETWEEN EFFECTIVE ARTERIAL PRESSURE AT BARORECEPTORS (PA1) AND CAROTID BARORECEPTOR EFFECT (AUCB). (FUN 9)
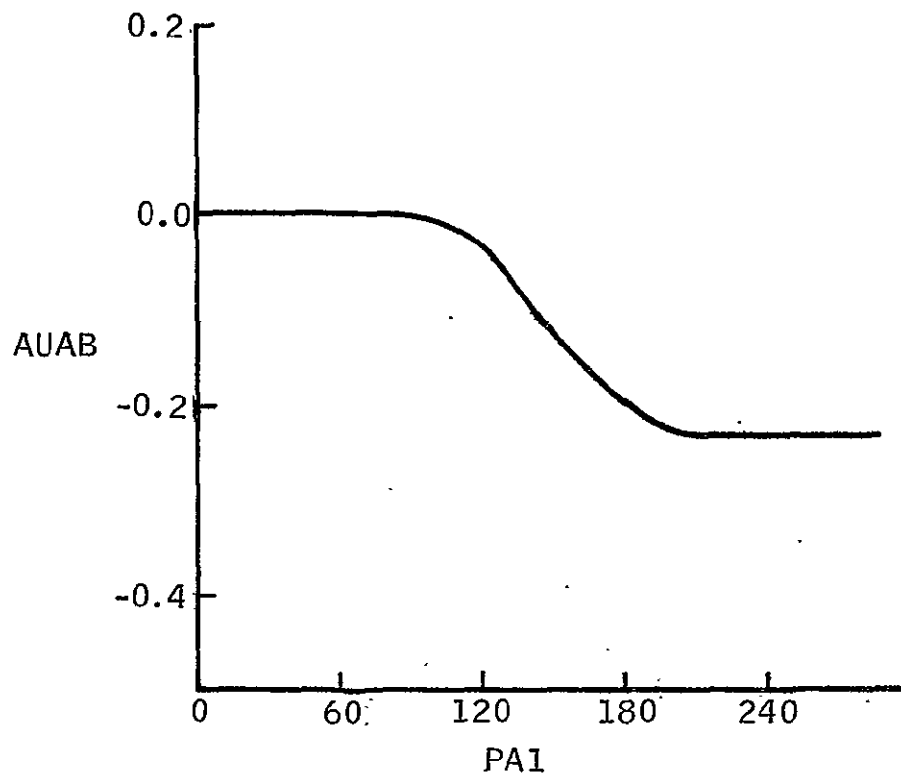
FIGURE 5. RELATION BETWEEN EFFECTIVE ARTERIAL PRESSURE AT
BARORECEPTORS (PA1) AND AORTIC BARORECEPTOR
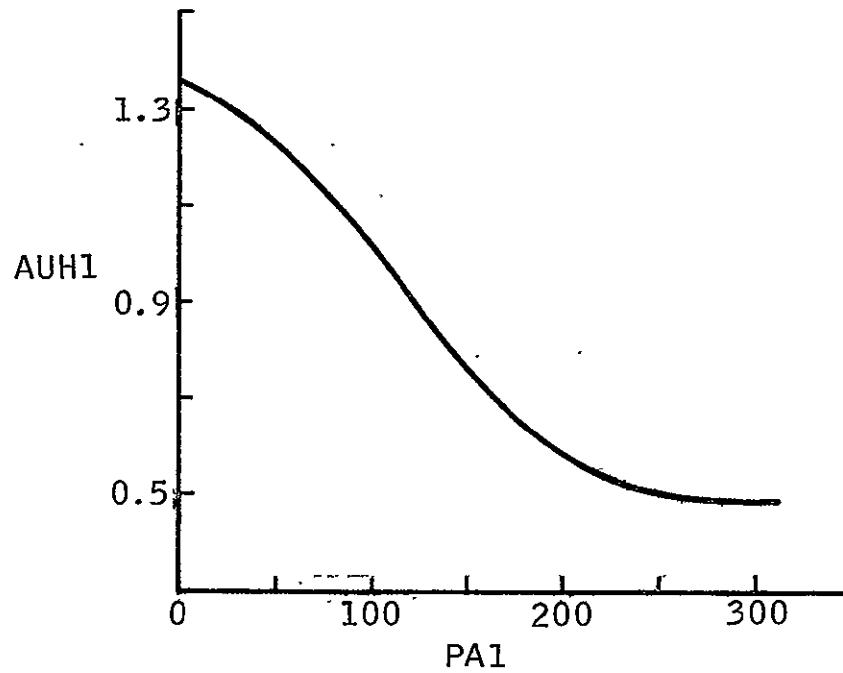EFFECT (AUAB). (FUN 10)

FIGURE 6. RELATION BETWEEN EFFECTIVE ARTERIAL PRESSURE AT
          BARORECEPTORS (PA1) AND AUTONOMIC EFFECT ON
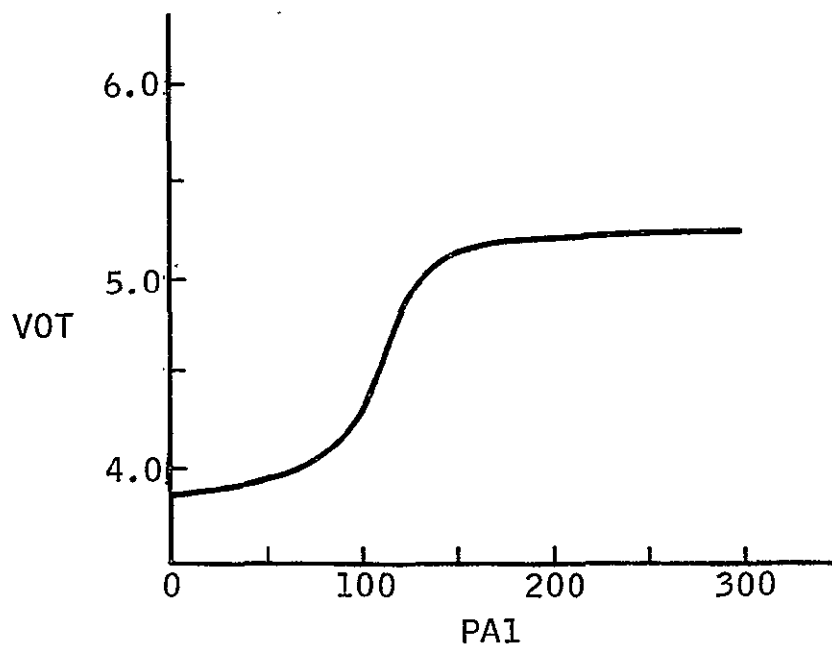   CARDIAC CONTRACTILITY (AUH1). (FUN 11)

FIGURE 7. RELATION BETWEEN EFFECTIVE ARTERIAL PRESSURE AT
BARORECEPTORS (PA1) AND TOTAL UNSTRESSED VASCULAR
VOLUME (VOT). (FUN 12)

APPENDIX A

GLOSSARY OF TERMS

The following is a list of all variables recently added to the long-term model together with normal values for these variables. Independent variables are indicated by * .

A*   –   sensitivity of suppressive effect of angiotensin on renin secretion (0. 15)

AKA*   –   damping factor involved in angiotensin production (10. 0)

AMS   –   short-term muscle autoregulatory effect (1. 0). (This was formerly called AMM.)

AM2   –   intermediate-term muscle autoregulatory effect (1. 0)

ANAR*   –   sensitivity of angiotensin effect on afferent arteriolar resistance in the kidney (0. 1)

ANCN*   –   normal angiotensin concentration in plasma (25.9 ng/l)

ANER*   –   sensitivity of angiotensin effect on efferent arteriolar resistance in the kidney (0. 1)

ANGS   –   fractional suppression of renin secretion influenced by angiotensin concentration (0.)

ANGT*   –   time constant for attainment of angiotensin suppression of renin (360. min)

ANK   –   angiotensin effect on tubular reabsorption (1. 0)

ANMM*   –   maximum effect of angiotensin (2. 5)

ANSS   –   steady-state fractional renin suppression caused by angiotensin (0.)

ANTC*   –   exponential parameter used to obtain angiotensin dose-response curve (3. 94)

AN2   –   angiotensin II amount (82. 5 ng)

AN3   –   parameter used to obtain angiotensin dose-response curve (1.93)

ATH*   –   sensitivity of angiotensin effect on thirst and salt intake (0. 058)

AUAB   –   autonomic response of aortic baroreceptors (0.)

AUCB   –   autonomic response of carotid baroreceptors (0.)

AUH1   –   initial response of pressure effect on contractility (1. 0)

AUH2   –   adapted response of contractility due to pressure (1. 0)

APPENDIX A   (Cont'd)

GLOSSARY OF TERMS

AUH3   –   extent of adaptation of contractility response due to pressure (1. 0)

A5K*   –   time constant for intermediate-term muscle autoregulation (1000. min)

B*   –   sensitivity of suppressive effect of renal tubular sodium flow on renin secretion (0. 15)

CAA*   –   time constant for angiotensin destruction (1. 0 min)

CAB*   –   sensitivity of total baroreceptor effect on aortic baroreceptors (3. 0)

CAIV*   –   angiotensin infusion rate (0. 0)

CAS*   –   rate constant for angiotensin production from renin (0. 0825)

CCB*   –   sensitivity of total baroreceptor effect on carotid baroreceptors (3. 0)

CRA*   –   time constant for renin destruction (0. 0655)

DESC*   –   delay in renal response used during salt loading (0.)

GP1*   –   sensitivity of angiotensin effect on renal tubular reabsorption (0. 215)

KO*   –   controlled value for potassium excretion (0.)

NAO*   –   controlled value for sodium excretion (0.)

POF   –   sensitivity control for intermediate-term muscle autoregulatory loop (1. 0)

POU*   –   sensitivity of intermediate-term muscle autoregulation (0. 05)

RC   –   plasma renin concentration   (1000. ng/l)

RNA*   –   controlled intake rate of sodium (0.)

RNK*   –   damping factor involved in renin production (30. 0)

RNS   –   rate of renin secretion per gram of kidney (0. 71 ng/min)

RSR   –   total rate of renin secretion for 300 grams of kidney (213 ng/min)

RT   –   total renin amount in plasma (3179 ng)

RTR*   –   controlled infusion rate of water (0.)

SRL*   –   time constant for intermediate vascular stress relaxation (360. min)

SRM*   –   time constant for long-term vascular stress relaxation (20160. min)

SR1*   –   intensity factor for intermediate vascular stress relaxation (0. 25)

SR2*   –   intensity factor for long-term vascular stress relaxation (0. 25)

UOC*   –   delay time constant for kidney during salt loading (960.)

APPENDIX A (Cont'd)

GLOSSARY OF TERMS

VASO — unstressed volume of arterial compartment (0.495 1)

VIL* — controlled insensible water loss rate (0.)

VINT* — controlled intake rate for water (0.)

VLAO — unstressed volume of pulmonary venous and left atrial compartment (0.4 1)

VOB* — controlled urinary output rate (0.)

VOT — total body systemic unstressed volume (4.25)

VOT1 — initial arterial pressure effect on whole-body unstressed volume (4.25)

VOT2 — adapted arterial pressure effect on whole-body unstressed volume (4.25)

VOT3 — extent of adaptation of arterial pressure effect on whole-body unstressed volume (0.)

VPAO — unstressed volume of pulmonary arterial compartment (0.306 1)

VRAO — unstressed volume of right atrial compartment (0.1 1)

VUGF — urinary flow due to filtration (.025)

VVSO — unstressed volume of venous compartment (2.96 1)

V61 — rate of change of intermediate stress-relaxation effect (0.)

V62 — rate of change of long-term stress-relaxation effect (0.)

V71 — increased vascular volume caused by intermediate stress relaxation (0.)

V72 — increased vascular volume caused by long-term stress relaxation (0.)

X6* — weighting factor for short-term vascular stress relaxation (0.8)

X7* — weighting factor for intermediate-term vascular stress relaxation (0.4)

X8* — weighting factor for long-term vascular stress relaxation (1.0)

APPENDIX B

ACID-BASE HOMEOSTASIS IN THE HUMAN SYSTEM

A Study Report

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I.   Introduction

Homeostasis, which has been termed "the central theorem of the physiology of the intact higher animal organism" (1), is manifest continually in the human through the response of the total collection of subsystems of the body to normal and abnormal challenges.   One of the most vigorously defended parts of the human system concerns acid-base balance and pH regulation, presumably because of the importance of such regulation to the myriad of biochemical reactions occurring in the cells (2).   Indeed, death follows with certainty, if pH regulation is not maintained at near normal capacity.

Acid-base regulation is a cooperative phenomena _in vivo_ with body fluids, extracellular and intracellular buffers, lungs, and kidneys all playing important roles.   The present account is much too brief to be considered a review of present knowledge of these regulatory systems, and should be viewed, instead, as a guide to the elements necessary to construct a simple model of the mutual interactions of the acid-base regulatory systems of the body.   More detailed information is available elsewhere (1, 3-8).

II.   Cells

Whole-body intracellular space is an extremely inhomogenous fraction of the body with wide diversity in both function and form.   In an ideal sense only, which may be useful as a first approximation, however, cell space may be characterized by average results weighted in some appropriate manner.

Thus, metabolic reactions in the cells produce large quantities of carbon dioxide and smaller quantities of other acid end products.   It is estimated that normal metabolic formation of carbon dioxide is approximately

200 ml/min (STPD) or 8.98 mmol/min (1 mmol CO_2 = 22.26 ml CO_2), while

production of other acids amounts to only 50-100 mmol/day, or 0.035 - 0.07

mmol/min (9). The cells contain chemical buffer systems capable of serving

as intermediate storage reservoirs of these acid end products, but in a nor-

mal balance situation the acid produced is transmitted to the interstitial

fluid and thus to the blood to be excreted by the lungs and kidneys.

The main chemical buffers of the cells are proteins, organic phosphates,

bicarbonate, and bone carbonate. Bone is generally differentiated from other

intercellular forms and considered by itself. The contribution of bone to

acid-base homeostasis is potentially large but generally not well understood

except in extreme cases (10). Bone will be treated only cursorily in most

of what follows. Concentrations appropriate to tissue intracellular space

(not bone) appear to be (11)

<div style="text-align:center">

bicarbonate: 10 mmol/L,
phosphates: 100 mmol/L,
proteins: 60 mmol/L.

</div>

In view of the fact that intracellular volume is approximately 25 L, the

stores of cellular buffer anions are large.

The red blood cells, (erythrocytes) have their own distinct function

to perform in acid-base control and they will be considered in more detail in

the section on blood. Their volume is approximately 2 L, although the water

content of red cells is only 1.3 L, if a protein content of 35% is assumed.

During acute and chronic attacks of both respiratory and metabolic

(non-carbon dioxide) components of acid-base balance, there is no doubt about

the participation of the cell in homeostatic response (12-16), but the nature

of the response in some cases is mechanistically unclear (17). This point

will be discussed later in relation to a simple model.

Under the normal conditions, the average pH of the cell seems to be

about 7.0 (18). The cell membrane is generally assumed to be highly

permeable to carbon dioxide gas with the P_{CO_2}=45-50 mm Hg at equilibrium.

The permeability of the membrane to bicarbonate or hydrogen ions is gener-

ally regarded as being somewhat less (6, 19, 20).

III. Interstitial Fluid

The interstitial fluid which lies between the cells consists of a small

amount of free fluid (0.5 L) and a large portion held in a gel (11.5 L).

For most purposes connected with acid base balance, the interstitial fluid

behaves as if the water were all free. Almost all dissolved substances,

with the exception of protein, move freely between the plasma and the inter-

stitial fluid through the capillary pores and perfect mixing can generally be

assumed for most substances. In this way, the cells are able to communicate

almost directly with other parts of the body through the blood. In a similar

way, the plasma has a large reservoir of materials at its disposal to assist

in "buffering" changes which occur locally. Thus, with the exception of

protein, the constituents of interstitial fluid should be very similar to

plasma. This is indeed found to be the case, but the concentration of various

ions are unequal in interstitial space and plasma due to the Donnan or Gibbs-

Donnan effect. It is easy to show that in the presence of a non-diffusable

charged ion on one side of a membrane, all other diffusible charged ions

(not pumped or otherwise effected) must distribute themselves unequally on

the two sides of the membrane (21).

The only buffer of any real significance in interstitial space is bi-

carbonate whose concentration in interstitial water is determined from the

corresponding concentration in plasma water by the relation

$$[HCO_3^-]_{ISF} = r [HCO_3^-]_P \tag{1}$$

where [$\cdots$] denotes concentration in mmol/L H_2O and r is the experimentally

determined Donnan factor, generally assumed to be 1.05 for anions

(21). Note that the concentrations here are relative to liters ($\sim$ kilo-

grams) water, not plasma volume. Thus, due to the presence of 7% pro-

tein in plasma $V_{P, H_2O} = 0.93 \, V_P$. For interstitial fluid (2% protein)

the correction is usually negligible.

A second buffer system exists in interstitial fluid, the phosphate

system ($H_2PO_4^-$, $HPO_4^=$). The total buffering power of this system is usually

negligible in comparison with the bicarbonate system _in vivo_ and will

generally be neglected in what follows. Less than 1% of the buffering is

accomplished by the phosphate system in most circumstances.

IV. Blood

Blood consists of two parts, an extracellular fluid of about 3 L volume

and 7% protein, and a cellular part of about 2 L volume and 35% protein. The

red cell membrane is permeable to all normal ionic species except protein.

The major constituents of plasma relative to acid-base functions _in_

vivo are bicarbonate and protein. Both of these substances act as buffers

for hydrogen ion changes, with the bicarbonate being the more important.

Plasma concentrations of bicarbonate and the various protein forms differ in

the various parts of the systemic circulation due to local changes in relative

portions of oxygen, carbon dioxide, and hydrogen ion carried in the blood.

In normal arterial plasma, pH = 7.4, $[CO_2] = 1.2$ mmol/L, and $[HCO_3^-] =$

24 mmol/L, on the average. In venous plasma, typical figures might be

pH = 7.37, $[CO_2] = 1.35$ mmol/L, and $[HCO_3^-] = 25.1$ mmol/L

Erythrocytes, on the other hand, contain hemoglobin in addition to

bicarbonate, and it is hemoglobin which plays the principal role in carbon

dioxide, as well as oxygen, transport. On the average, 34 g. of hemoglobin is contained in 100 ml. of red cells and with a normal hematocrit of about 40, blood usually contains about 15 g. of hemoglobin per 100 ml. These values may have considerable local variation. The protein hemoglobin _in vivo_ has a net negative charge. It is capable of combining with, and thereby transporting, both oxygen and carbon dioxide, and at the same time is capable of buffering hydrogen ions. The molecular weight of hemoglobin is approximately 68,000 g. and one mole of hemoglobin is capable of combining with four moles of oxygen. It is usual to measure hemoglobin amounts either in grams or in milliequivalents on an oxygen basis. Thus, 1 mole of hemoglobin contains 4 equivalents of hemoglobin (or 1 milliequivalent weight(meq) of hemoglobin = 16.7 g.). Hemoglobin combined with oxygen to its fullest extent is called oxyhemoglobin and will be denoted "HbO_2" while hemoglobin carrying no oxygen is called reduced hemoglobin and will be denoted "Hb". The negative charge will be suppressed. Each gram of hemoglobin is capable of carrying approximately 0.06 mmol of oxygen (or 1.34 ml STP) at full saturation. The fraction saturation of hemoglobin is the fraction of hemoglobin in the blood that is in the form HbO_2. This fraction varies from 0.97 for arterial blood down to about 0.70 for venous blood (under normal resting conditions). The relation between the saturation level (usually expressed as per cent saturation) and the oxygen partial pressure is expressed by the oxygen dissociation curve of hemoglobin (22).

In general, a buffered solution is one which tends to maintain a constant pH in the face of challenge by acid additions or withdrawals. Such a solution contains appreciable concentrations of various weak acids and their cooresponding highly ionized "salts". For example, consider a solution containing 0.1 mole/L sodium acetate and 0.05 mole/L acetic acid (at 25°C).

The pH is approximately

$$pH = 4.57 + \log \left[\frac{0.1}{0.05}\right] = 4.87.$$

Addition of 0.01 mole of hydrochloric acid to a liter of this solution would lead to an approximate new pH given by

$$pH = 4.57 + \log \left[\frac{0.09}{0.06}\right] = 4.75.$$

Addition of this same quantity of acid to a liter of pure water (pH = 7.) leads to a new pH of 2. The resistance of the buffer solution to pH changes is clear.
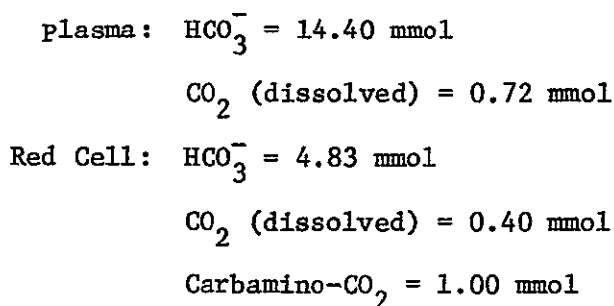
As stated above hemoglobin serves as a buffer (not the only one) in blood. In fact both oxyhemoglobin and reduced hemoglobin have buffering abilities. The presence of oxygen makes the oxyhemoglobin a stronger acid than reduced hemoglobin and consequently the reduced hemoglobin is a better buffer than oxyhemoglobin. The body uses this fact to good advantage since oxygen is given up and acidic waste picked up in the tissue. The buffering ability of a solution is generally expressed by means of its titration curve which is the relation between the amount of acid added to the solution and the pH of the solution. The experimentally important variable is the slope of the titration curve and the term "buffer value" is usually defined as the negative of the slope of the titration curve (5). The units of buffer value are usually mmol/liter/pH unit and this unit is termed a slyke (sl) (5). The buffer value of a solution containing more than one buffer substance is the sum of the buffer value of each substance. The buffer value of each substance is directly proportional to the concentration of that substance.

Transportation of carbon dioxide from the tissues to the lungs is effected by both the plasma and the red cells. In general, carbon dioxide diffuses through the interstitial space into the plasma and red cells. A small amount of carbon dioxide gas dissolves in the plasma and an even smaller
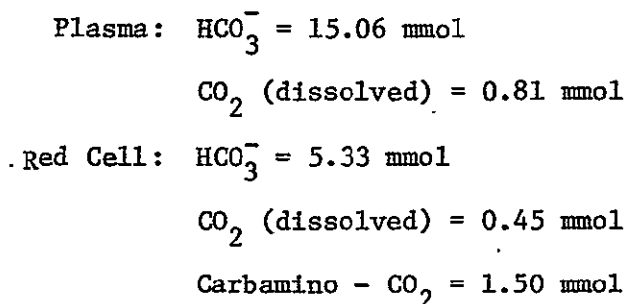
amount forms a direct carbamino compound with plasma proteins. Some of the

dissolved CO_2 reacts with water to form carbonic acid which ionizes slightly

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-. \qquad (2)$$
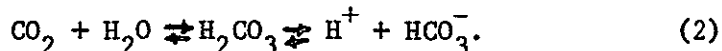
The carbon dioxide diffusing into the erythrocytes remains partially dissolved

but the largest portion of that which enters either combines directly with

hemoglobin to form carbamino - CO_2 or hydrolyzes under carbonic anhydrase

catalysis to form carbonic acid which ionizes to a great extent. This

ionization takes place because the H^+ ions produced are buffered by the

hemoglobin, and then the HCO_3^- ions largely diffuse back into the plasma.

The carbonic anhydrase present allows the hydrolysis reaction to proceed

sufficiently rapidly that equilibrium is attained almost instantaneously.

Thus, the major forms of carbon dioxide in the plasma are dissolved carbon

dioxide and bicarbonate, and in the red cell are dissolved carbon dioxide,

carbamino - CO_2, and bicarbonate. Typical average values for carbon dioxide

distribution in one liter of normal arterial blood would be

plasma: HCO_3^- = 14.40 mmol

CO_2 (dissolved) = 0.72 mmol

Red Cell: HCO_3^- = 4.83 mmol

CO_2 (dissolved) = 0.40 mmol

Carbamino-CO_2 = 1.00 mmol

In normal venous blood corresponding values would be

Plasma: HCO_3^- = 15.06 mmol

CO_2 (dissolved) = 0.81 mmol

Red Cell: HCO_3^- = 5.33 mmol

CO_2 (dissolved) = 0.45 mmol

Carbamino - CO_2 = 1.50 mmol

Thus plasma bicarbonate is the major carbon dioxide carrier, but the distri-

bution depends greatly on the presence of the red cell with its carbonic
anhydrase and hemoglobin.·

V. Respiratory System

The major acid end product of metabolism, carbon dioxide, is produced
by the body at the rate of about 200 ml/min at rest. Each day a minimum
of about 300 liters of carbon dioxide is generated and in a steady state
precisely this amount must be disposed of. It is one of the major functions
of the respiratory system to effect this disposal. By the respiratory sys-
tem is meant the lungs together with their controlling center in the brain and
nervous system. Normally, except during exercise, arterial P_{CO_2} is the
main stimulus to control of alveolar ventilation. This stimulus appears to
be due to neural impulses transmitted from two distinct sets of receptors:
central receptors located in the brain-cerebrospinal fluid region, and in peri-
pheral receptors located mainly in the carotid and aortic bodies (23, 24).
The exact cause of the stimulus is difficult to determine, but either P_{CO_2}
itself or hydrogen ion level (in a non-hypoxic state) would suffice with hy-
drogen ion level more likely centrally. The peripheral receptors seem to
account for somewhat less of the respiratory response than the central receptors.

Basically, if arterial P_{CO_2} rises, arterial hydrogen ion levels increase
slightly which stimulates the peripheral receptors to increase firing and
stimulate respiration to some extent. The major response, in this case,
is due to the response of the central receptors. An increase in arterial
P_{CO_2} causes a P_{CO_2} shift in the interstitial fluid of the brain due to the
lipid solubility of carbon dioxide. Cerebrospinal and interstitial fluid
are not as well buffered as the blood and a barrier to rapid exchange of
buffers (mainly bicarbonate) between these systems prevents ion equilibration
from occurring rapidly. Thus the P_{CO_2} increase in the central area causes

a much larger hydrogen ion change there and a correspondingly larger increased stimulation to ventilation. This stimulation disappears with time as bicarbonate adjustments are made which allow the pH to return to normal and the main stimulus reverts to the peripheral receptors. The increased ventilation tends to reduce the arterial P_{CO_2} completing the feedback loop.

When hydrogen ion concentration rises peripherally due to addition of non-volatile acid, alveolar ventilation is stimulated because of the increased activity of the peripheral receptors. The fall in carbon dioxide levels is transmitted centrally and causes a competitive depression of the ventilation. As time passes, central adjustments in bicarbonate levels are made which allow alveolar ventilation to increase. This increase in ventilation tends to drive arterial pH back to normal.

VI. Renal System

Addition of acidic substances other than carbon dioxide or of substances with basic properties to the blood causes deviations in hydrogen ion, bicarbonate and carbon dioxide levels from normal and compensation for these deviations cannot be completely made by the buffering systems of the body discussed up to now (the respiratory system may be considered a physiological buffer). It is the role of the renal system to effect complete compensation. The active, constant role the kidney plays even in normal states is, in fact, large and important. With a normal glomerular filtration rate of 125 ml/min and a plasma bicarbonate level of 24 mmol/l, 3 millimoles of bicarbonate are filtered each minute. If this were not almost completely reabsorbed, the body would rapidly be depleted of one of its most important chemical buffers. In fact, bicarbonate seems to be completely reabsorbed, in effect, by the body in the normal state.

Renal reabsorption of bicarbonate is accomplished as a result of the interaction between hydrogen ion actively secreted by the tubules and filtered bicarbonate with consequent diffusion of the resulting carbon dioxide back into the cells where hydration leads to bicarbonate reformation. The source of the original hydrogen ions secreted is not clear, but it is clear that the process is extremely carbon dioxide sensitive. On a phenomenological level, the renal clearance (excretion rate/plasma concentration) of bicarbonate appears to exhibit a threshold occurring at a plasma concentration of approximately 24 - 28 mmol/l. The maximal tubular reabsorptive capacity per unit volume of glomerular filtrate thus determined is about 2.4 - 2.8 meq/100 ml of glomerular filtrate with arterial P_{CO_2} = 40 mm Hg and increases with increasing arterial P_{CO_2}. This apparent threshold now seems to be an artifact of the experimental technique used in its measurement and the current view is that a complex interaction between extracellular volume, potassium, and adrenal steroids control bicarbonate reabsorption (25).

The kidney's fundamental method of reaction to increased acid loads in the body must be such as to not only reabsorb filtered bicarbonate but also to generate new bicarbonate at an enhanced level. During an acid load plasma-bicarbonate level falls and hence filtered bicarbonate decreases. Acid secretion (hydrogen ion) by the tubules continues at a relatively enhanced level determined by blood P_{CO_2}. For each hydrogen ion secreted a bicarbonate ion is generated in peritubular blood. The secreted hydrogen ions are transported to the urine by formation of ammonium ions and by combination with phosphate buffers. Thus the acidosis is corrected. The process continues until the normal state is attained (if possible), but total com-

pensation takes from one to several days. With an increasing base load, plasma bicarbonate rises increasing filtered bicarbonate. Once acid secretion is exceeded, progressive amounts of bicarbonate are lost directly in the urine and correction follows.

VII. Acid-Base Abnormalities

Modern clinical terminology for disturbances in acid-base regulation is as follows (5). Acidosis refers to an abnormal physiological process characterized by gain of acid or loss of base by the extracellular fluid of the body. Alkalosis is an abnormal physiological process characterized by gain of base or loss of acid by the extracellular fluid of the body. The prefix metabolic (metabolic acidosis, metabolic alkalosis) is used to denote abnormal processes characterized by primary gains or losses of strong acid, strong base, or bicarbonate from the extracellular fluid. The prefix respiratory (respiratory acidosis, respiratory alkalosis) refers to abnormal processes in which there are primary changes in the rate of alveolar ventilation relative to the rate of carbon dioxide production.

Abnormalities in blood acid-base parameters, which are taken to be pH, bicarbonate concentration, and P_{CO_2} of plasma, are characterized by the following terms. Acidemia means pH is lower than normal. Alkalemia means pH is higher than normal. Hypobasemia means bicarbonate concentration is lower than normal while hyperbasemia means bicarbonate concentration is higher than normal. Hypocapnia and hypercapnia refer to a decreased or increased level of P_{CO_2} relative to normal.

The abnormal physiological processes, acidosis and alkalosis, may lead to a variety of different abnormalities in the blood acid-base parameters due to the secondary or compensatory reactions of the body to the primary disturbance.

A gain of strong acid or a loss of strong base or bicarbonate from the extracellular fluid all lead to a fall in the concentration of bicarbonate in the extracellular fluid. This fall is the prime abnormality of metabolic acidosis. In acid loading the bicarbonate level falls because of the buffering of the acid by the bicarbonate. The body responds to this loss of bicarbonate in several ways. The cell fluids effectively transfer bicarbonate into the extracellular space either directly by bicarbonate movement or indirectly by hydrogen ion uptake or by both processes. The respiratory system responds by adjusting P_{CO_2} to a lower value. The renal system responds by effectively generating new bicarbonate through acid secretion.

In metabolic alkalosis the primary disturbance is due to a gain of bicarbonate or loss of acid (gain of base) by the extracellular fluid. Since the loss of acid is buffered by the bicarbonate system, in either case a gain of bicarbonate occurs. Cells respond by transferring hydrogen ions into extracellular fluid thus eliminating some bicarbonate. The respiratory system increases P_{CO_2}. The renal system rather rapidly raises excretion of bicarbonate.

In respiratory acidosis, alveolar ventilation is decreased relative to the rate of carbon dioxide production. Carbon dioxide levels in the body increase leading to a fall in pH. The buffer systems respond to the decreased pH and bicarbonate levels increase. The kidney increases its excretion of titratible acid and ammonia and thus raises bicarbonate levels even further. These responses tend to raise pH.

With respiratory alkalosis, alveolar ventilation rises relative to carbon dioxide production leading to a primary loss of carbon dioxide. This causes pH to rise. The buffer system acts to retard the rise by reducing

bicarbonate levels in the body and the renal system by excreting bicarbonate in the urine. In this way pH tends to fall.

VIII. A Simple Model

In this section a quantitative approach to acid-base homeostasis is presented which incorporates much of the data and experimental findings outlined in the preceding sections. This approach will utilize a modeling format as it is intended to include the resultant model as a subsystem model in a more complete analysis of overall circulatory regulation. In fact, the current intention is to use a presently available circulatory model (26) as the main component of a much larger model with systems such as the acid-base homeostatic system discussed here being added at a later date. With this in mind, many circulatory variables may be assumed known as the large model will provide values for these. Such variables include cardiac output, hematocrit, oxygen consumption, cell volume, etc. A second point worthy of mention in this connection is the fact that the overall model is basically designed for the study of intermediate to long term effects and that the present model must be adequate for the representation of experiments of days to weeks duration. Previous models which have considered acid-base response have not been adequate for simulation of even a one day response.

The present model consists of a compartmental approach with seven distinct compartments. These are chosen as lungs, brain, cerebrospinal fluid, tissue (non-brain) intracellular space, tissue (non-brain) extracellular space, arterial blood and mixed venous blood. The kidneys are represented explicitly only in their effect on bicarbonate reabsorption and new bicarbonate production. The assumption is made that the carbon dioxide buffer

curve (or equivalently the carbon dioxide dissociation curve) represents
the steady-state situation and serves also as an adequate predictor of
the steady state during transient events. Hypoxia will not be of interest
here and the dynamics of the oxygen system will be kept very simple, just
as they are in the large circulatory model.

To begin with, consider the situation in the tissue (non-brain) in-
tracellular space (IC). Let B_{IC} represent the bicarbonate concentration
of this compartment in mmol/l, P_{IC} the partial pressure of CO_2 in mm Hg,
MC_{IC} the total metabolic production of CO_2 in all forms in mmol/min, MH_{IC}
the effective net metabolic rate of formation of hydrogen ion in mmol/min,
W_{IC} the total concentration of CO_2, BS_{IC} the concentration of bicarbonate
at pH = pHS_{IC}. Corresponding definitions hold for tissue (non-brain)
extracellular space and the subscript EC is used to denote these. Then
the conservation equations become

$$\frac{d}{dt}[V_{IC}\ W_{IC}] = MC_{IC} + k_1(P_{EC} - P_{IC}) + k_2(B_{EC} - B_{IC}) - MH_{IC}, \qquad (3)$$

and

$$\frac{d}{dt}[V_{IC}\ BS_{IC}] = k_2(B_{EC} - B_{IC}) - MH_{IC}. \qquad (4)$$

These equations are to be used in conjunction with the CO_2 buffer or dissocia-
tion equation for the compartment which is

$$W_{IC} = BS_{IC} - \beta_{IC}\left\{pH_{IC} - pHS_{IC}\right\} + A_{IC}P_{IC} \qquad (5)$$

where

$$pH_{IC} = pK_{IC} + \log\left[\frac{W_{IC} - A_{IC}\ P_{IC}}{A_{IC}\ P_{IC}}\right]. \qquad (6)$$

The first term on the right side of Equation (3) represents metabolic produc-
tion of CO_2, the second term represents diffusion of CO_2 from extracellular
space, the third term represents "net effective bicarbonate flux" from extra-
cellular space, and the last term represents "net metabolic hydrogen ion pro-
duction". The effect of these last two terms is to raise or lower the bi-

carbonate concentration at fixed pH and Equation (4) represents this fact.

In Equation (5) the total carbon dioxide concentration is obtained by

summing the bicarbonate concentration and the non-bicarbonate CO_2 concen-

tration. Bound CO_2 amounts (carbamino compounds) are assumed negligible

here. The slope of the CO_2 titration curve is given by β_{IC} and is assumed

constant for this compartment. Note that

$$B_{IC} = BS_{IC} - \beta_{IC} \left(pH_{IC} - pHS_{IC} \right). \tag{7}$$

Typical values for the constants appear to be $k_1 = 3.0$, $k_2 = 0.0027$,

$pHS_{IC} = 7.0$, $A_{IC} = 0.03$, $pK_{IC} = 6.1$, and $\beta_{IC} = 15$. These values were chosen

so that when $MC_{IC} = 9.0$, $MH_{IC} = 0.04$, $P_{EC} = 45$, and $B_{EC} = 25.87$ a steady

state obtains with $B_{IC} = 11.3$, $P_{IC} = 48.$, and $pH_{IC} = 7.0$. For the tissue

(non-brain) extracellular space (EC), the conservation equations become

$$\frac{d}{dt}[V_{EC} W_{EC}] = Q_{EC}(W_{AB} - W_{VB}) - k_1(P_{EC} - P_{IC}) - k_2(B_{EC} - B_{IC}) + R_B, \tag{8}$$

and

$$\frac{d}{dt}[V_{EC} BS_{EC}] = R_B - k_2(B_{EC} - B_{IC}) \tag{9}$$

and the corresponding CO_2 buffer or dissociation equation including the

Haldane effect is

$$W_{EC} = BS_{EC} - \beta_{EC} \left\{ pH_{EC} - pHS_{EC} \right\} + k_3 Hb(1-S_{VB}) + A_{EC} P_{EC} \tag{10}$$

with

$$pH_{EC} = pK_{EC} + \log \left[\frac{W_{EC} - A_{EC} P_{EC}}{A_{EC} P_{EC}} \right]. \tag{11}$$

In these equations Q_{EC} represents the blood flow to the tissues (non-brain),

R_B represents the net renal generation of bicarbonate, Hb represents the

hemoglobin concentration in gram % (g/100 ml blood), S_{VB} represents the

fractional oxygen saturation of the hemoglobin, W_{AB} represents the total

CO_2 content of arterial blood, and W_{VB} represents the total CO_2 content of

venous blood draining the tissues. It is assumed that the venous blood and

extracellular space are in equilibrium · ¯ an effects are ignored. Then

$W_{VB} = W_{EC}$ and $P_{VB} = P_{EC}$. The slope of the titration curve, β_{EC}, is determined from the plasma and interstitial fluid protein levels and the amount of hemoglobin present in the blood. The relation is

$$\beta_{EC} = \frac{V_P \; PR_P}{V_{EC}} + \frac{V_I \; PR_I}{V_{EC}} + \frac{1.51 \; VB \; Hb}{V_{EC}} \tag{12}$$

where PR_p is the plasma protein concentration, PR_I is the interstitial fluid protein concentration, and Hb is the hemoglobin concentration in blood, all expressed in g% (grams/100 ml), and V_p is the plasma volume, VB the total blood volume, and V_I is the interstitial volume. Typical values for the new parameters are $k_3 = 0.09$, $pHS_{EC} = 7.38$, $A_{EC} = 0.03$, $S_{VB} = 0.7$, $pK_{EC} = 6.1$, $PR_p = 7.0$, $PR_I = 1.27$, Hb = 15.0 and $BS_{EC} = 25.5$. With these values a steady state obtains with $P_{EC} = 45.$, $B_{EC} = 25.87$, $R_B = 0.04$ when $Q_{EC} = 4.25$, and $W_{AB} = 25.1$.

For the brain (B) compartment no subdivision into extracellular and intracellular space is assumed. Instead, a cerebrospinal fluid (CSF) compartment is introduced which is able to rapidly exchange CO_2 with the brain by diffusion. A slow exchange (or pumping) of bicarbonate appears possible with the ultimate goal of CSF pH regulation. Thus, no (or only slight) bicarbonate flow seems to occur due to bicarbonate imbalance. Rather, the mechanism is an active extrusion or uptake to return pH to normal after CO_2 diffusion. For the brain, the appropriate balance equation is

$$\frac{d}{dt}[V_B W_B] = MC_B + Q_B(W_{AB} - W_{BVB}) + k_4(P_{CSF} - P_B) + BT \tag{13}$$

where MC_B represents total metabolic CO_2 production of the brain, and BT represents effective bicarbonate transfer into the brain from the CSF compartment. The CO_2 buffer curve is

$$W_B = BS_B - \beta_B \left\{ pH_B - pHS_B \right\} + A_B P_B \tag{14}$$

where the terms have their usual meaning. It is assumed that brain venous

blood (BVB) has the same P_{CO_2} as brain tissue itself, but a buffer curve is given by

$$W_{BVB} = BS_{BVB} - \beta_{BVB} \left\{ pH_{BVB} - pHS_{BVB} \right\} + k_5 Hb(1-S_{BVB}) + A_{BVB}P_B. \qquad (15)$$

The cerebrospinal fluid (CSF) compartment is taken to contain a solution of bicarbonate in water that rapidly exchanges CO_2 with the brain by diffusion, and slowly "pumps" bicarbonate to maintain steady state pH. Thus

$$\frac{d}{dt}[V_{CSF} A_{CSF} P_{CSF}] = k_4 (P_B - P_{CSF}) \qquad (16)$$

and

$$\frac{d}{dt}[V_{CSF} B_{CSF}] = - BT. \qquad (17)$$

The pH_{CSF} is then determined from

$$pH_{CSF} = pK_{CSF} + \log \left[\frac{B_{CSF}}{A_{CSF} P_{CSF}} \right]. \qquad (18)$$

It is assumed that BT is such that pH_{CSF} returns to normal, pHS_{CSF}, with time constant T_{CSF}. Thus, B_{CSF} approaches a steady state value BSS_{CSF} given by

$$BSS_{CSF} = A_{CSF} P_{CSF} 10^{(pH_{CSF} - pK_{CSF})}. \qquad (19)$$

In this case

$$BT = (BSS_{CSF} - B_{CSF})/T_{CSF}. \qquad (20)$$

Typical parameter values for the above equations are $MC_B = 2.25$, $Q_B = 0.75$, $W_{AB} = 25.1$, $W_{BVB} = 28.1$, $k_4 = 0.000365$, $P_{CSF} = 47.8$, $P_B = 47.8$, $BT = 0$, $BS_B = 27.3$, $\beta_B = 28.9$, $pH_B = 7.38$, $pHS_B = 7.38$, $A_B = 0.03$, $BS_{BVB} = 25.1$, $pH_{BVB} = 7.37$, $pHS_{BVB} = 7.37$, $k_5 = 0.3$, $Hb = 15$, $S_{BVB} = 0.66$, $V_{CSF} = 0.1$, $V_B = 1.0$, $A_{CSF} = 0.03$, $T_{CSF} = 1000.$, and $pK_{CSF} = 6.08$. The buffer power of blood is given by

$$\beta_{BVB} = \frac{V_P PR_P}{VB} + 1.51 \, Hb \qquad (21)$$

where Hb is the hemoglobin concentration in g/100 ml blood, and PR_P is the plasma protein concentration in g/100 ml plasma. The quantity BS_{BVB} also changes as "effective bicarbonate" is exchanged with cell space through the equation

$$\frac{d}{dt} BS_{BVB} = \frac{\overset{\cdot}{R}_B - k_2(B_{EC} - B_{IC})}{V_{EC}}. \qquad (22)$$

Note that V_{EC} is assumed constant, an assumption which introduces no significant error.

The mixed venous blood entering the lung consists of a weighted average of venous blood from the brain and from the tissue areas. If Q is the total cardiac output

$$W_{MV} = \frac{Q_{EC}}{Q} W_{EC} + \frac{Q_B}{Q} W_{BVB}. \qquad (23)$$

Normally $W_{MV} = \frac{4.25}{5.} \times 27.2 + \frac{0.75}{5.} \times 28.1 = 27.3$ meq/l.

In the lung reservoir the mass balance equation for CO_2 is

$$\frac{d}{dt}[V_L F_A] = V_A \left\{ F_I - F_A \right\} + 0.0269 \ Q \left\{ W_{MV} - W_{AB} \right\}. \qquad (24)$$

This equation is derived by neglecting the difference between inspired and expired ventilation. F_A is the volumetric fraction of CO_2 in dry alveolar gas, F_I is the corresponding volumetric fraction in dry inspired gas, V_A is alveolar ventilation in l/min (BTPS), V_L is the effective alveolar volume, and the 0.0269 is a conversion factor which changes meq/min total CO_2 flow to l/min flow at BTPS. In fact

$$- \ 22.26 \ \frac{ml}{meq} \ \times \ \frac{1 \ 1}{1000 \ ml} \ \times \ \frac{760}{713} \ \times \ \frac{310}{273} \ = 0.0269$$

since STPD means P = 760 mm Hg, T = 273°K and BTPS means P = 760 − 47 = 713 mm Hg, T = 273 + 37 = 310°K at sea level. The relation between volumetric fraction and partial pressure is

$$P_A = 713 \ F_A \qquad (25)$$

at sea level. It is assumed that arterial P_{CO_2} equals alveolar P_{CO_2}, P_A.

Then at equilibrium V_A = 5.27 1/min, F_A = 0.056 or P_A = 40. Knowledge of

P_A allows computation of W_{AB} through the buffer or dissociation equation

$$W_{AB} = BS_{AB} - \beta_{AB}\left\{pH_{AB} - pHS_{AB}\right\} + k_5 \, Hb(1-S_{AB}) + A_{AB}P_A. \qquad (26)$$

Here $\beta_{AB} = \beta_{BVB}$ (Equation (21)), BS_{AB} = 23.9, pHS_{AB} = 7.4, k_5 = 0.3,

S_{AB} = 0.99, and A_{AB} = 0.03. BS_{AB} changes with the same rate as BS_{EC} and

BS_{BVB}, therefore

$$\frac{d}{dt} \, BS_{AB} = \frac{R_B - k_2(B_{EC} - B_{IC})}{V_{EC}} \qquad (27)$$

Alveolar ventilation itself must be determined from a controller equation like

$$V_A = C_1 pH_{AB} + C_2 pH_{CSF} + C_3. \qquad (28)$$

Renal function enters this model only through the net renal generation

of extracellular bicarbonate R_B. This includes net reabsorption and net

generation through titratable acid and ammonia secretion. The amount of

bicarbonate filtered at the kidney is given by

$$\text{AMT. FILTERED} = GFR \, (W_{AB} - A_{AB}P_A) \qquad (29)$$

where GFR is the total glomerular filtration rate. Normally GFR = 0.125

1/min so that the amount filtered is approximately 3 meq/min. If

$W_{AB} - A_{AB}P_A$ (=B_{AB}) is less than T_M meq/1, all bicarbonate is reabsorbed (at

P_A = 40 mm Hg, T_M = 24). The value of T_M depends on arterial P_{CO_2} and it

is assumed that

$$T_M = 13.12 + 0.272 \, P_A, \quad P_A < 40$$
$$= 16.72 + 0.182 \, P_A, \quad P_A \geqslant 40. \qquad (30)$$

Thus if P_A rises, T_M rises and bicarbonate level rises buffering pH changes.

The bicarbonate lost by not being reabsorbed is

$$BA_L = GFR\left\{W_{AB} - A_{AB}P_A - T_M\right\} \qquad (31)$$

if $W_{AB} - A_{AB}P_A > T_M$ and is 0 otherwise.

Normal titrable acid secretion amounts to about 0.013 meq/min while nor-

mal ammonia secretion is 0.027 meq/min. The assumption is made that titra-

table acid excretion is 0.13 meq/min if $W_{AB} - A_{AB}P_A < 18$ and that $TA = 0$ if $W_{AB} - A_{AB}P_A > 24.5$. In between

$$TA = 0.486 - 0.0198(W_{AB} - A_{AB}P_A). \tag{32}$$

The response is assumed instantaneous. Ammonia excretion is assumed to have a steady state maximum of 0.3 meq/min if $W_{AB} - A_{AB}P_A < 18$, but there is a delay associated with attainment of that maximum with time constant T_{NH}. If $W_{AB} - A_{AB}P_A > 24.5$ ammonia excretion is assumed zero. The maximum ammonia excretion then takes the form

$$NH_3M = 1.126 - 0.046(W_{AB} - A_{AB}P_A) \tag{33}$$

otherwise. Actual ammonia excretion is simulated by the equation

$$\frac{d}{dt} NH_3 = (NH_3M - NH_3)/T_{NH} \tag{34}$$

if $NH_3M > NH_3$. If $NH_3 > NH_3M$ then $NH_3 = NH_3M$. This allows a rapid fall in ammonia production.

The basic model is complete. Much is left out and much remains to be discussed in detail. The influence of pH on other body functions has not been mentioned at all. It is this effect on the body that is the prime motivation for studying the systems that regulate pH. Ventilation control was only briefly mentioned. The effect of aldosterone, potassium, and chloride levels was not considered. Such a treatment would be unpardonable were it not meant to be a simple first effort. What remains is actual computer simulation coupled with a delineation of the effects of acid base imbalance on the major controller functions of the body.

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